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THE UNITED STATES OF AMERICA

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June 07, 2004

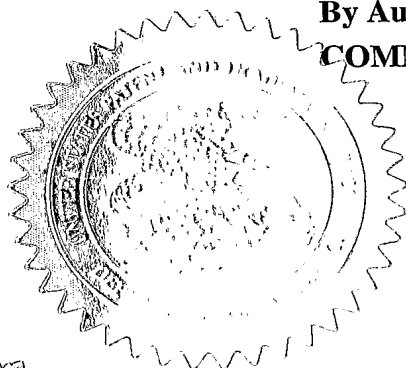
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APPLICATION NUMBER: 60/488,408

FILING DATE: July 21, 2003

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E. Bornett

E. BORNETT
Certifying Officer

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

INVENTOR(S)					
Given Name (first and middle (if any))	Family Name or Surname	Residence (City and either State or Foreign Country)			
MORDECHAI	DEUTSCH	MOSHAV OLESH, ISRAEL			
<input type="checkbox"/> Additional inventors are being named on the _____ separately numbered sheets attached hereto					
TITLE OF THE INVENTION (500 characters max)					
AN EXPANDABLE CELL CHIP MATRIX					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
<input type="checkbox"/> Customer Number		Type Customer Number here		Place Customer Number Bar Code Label here	
OR					
<input checked="" type="checkbox"/> Firm or Individual Name		SCHOTTENSTEIN CELLOME RESEARCH CENTER			
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City	RAMAT GAN	State		ZIP	52900
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ENCLOSED APPLICATION PARTS (check all that apply)					
<input checked="" type="checkbox"/> Specification		Number of Pages	6	<input type="checkbox"/> CD(s), Number	
<input checked="" type="checkbox"/> Drawing(s)		Number of Sheets	3	<input type="checkbox"/> Other (specify)	
<input type="checkbox"/> Application Data Sheet. See 37 CFR 1.76					
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT					
<input checked="" type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27.				FILING FEE AMOUNT (\$)	
<input checked="" type="checkbox"/> A check or money order is enclosed to cover the filing fees				\$80.00	
<input type="checkbox"/> The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number:					
<input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached.					
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
<input checked="" type="checkbox"/> No.					
<input type="checkbox"/> Yes, the name of the U.S. Government agency and the Government contract number are:					

Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME MORDECHAI DEUTSCH

TELEPHONE 97235344675

Date 07/21/2003

REGISTRATION NO.
(if appropriate)
Docket Number:

22

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

07/21/03

13281 U.S. P.T.O.

PTO/SB/17 (05-03)

Approved for use through 04/30/2003. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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**FEE TRANSMITTAL
for FY 2003**

Effective 01/01/2003. Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT

(\$)

80

Complete if Known

Application Number

Filing Date

First Named Inventor

MORDECHAI DEUTSH

Examiner Name

Art Unit

Attorney Docket No.

22

METHOD OF PAYMENT (check all that apply)☒ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None☐ Deposit Account:Deposit
Account
Number
Deposit
Account
Name

The Director is authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Credit any overpayments☐ Charge any additional fee(s) during the pendency of this application☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.**FEE CALCULATION****1. BASIC FILING FEE**

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1001 750	2001 375	Utility filing fee	
1002 330	2002 165	Design filing fee	
1003 520	2003 260	Plant filing fee	
1004 750	2004 375	Reissue filing fee	
1005 180	2005 80	Provisional filing fee	80

SUBTOTAL (1) (\$)

80

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Total Claims	Extra Claims	Fee from below	Fee Paid
Independent Claims	-20** =	X	
Multiple Dependent	-3** =	X	

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description
1202 18	2202 9	Claims in excess of 20
1201 84	2201 42	Independent claims in excess of 3
1203 280	2203 140	Multiple dependent claim, if not paid
1204 84	2204 42	** Reissue independent claims over original patent
1205 18	2205 9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)**3. ADDITIONAL FEES**

Large Entity Small Entity

Fee Code (\$)	Fee Code (\$)	Fee Description	Fee Paid
1051 130	2051 65	Surcharge - late filing fee or oath	
1052 50	2052 25	Surcharge - late provisional filing fee or cover sheet	
1053 130	2053 65	Non-English specification	
1812 2,520	2812 1,260	For filing a request for ex parte reexamination	
1804 920*	2804 460*	Requesting publication of SIR prior to Examiner action	
1805 1,840*	2805 920*	Requesting publication of SIR after Examiner action	
1251 110	2251 55	Extension for reply within first month	
1252 410	2252 205	Extension for reply within second month	
1253 930	2253 465	Extension for reply within third month	
1254 1,450	2254 725	Extension for reply within fourth month	
1255 1,970	2255 985	Extension for reply within fifth month	
1401 320	2401 160	Notice of Appeal	
1402 320	2402 160	Filing a brief in support of an appeal	
1403 280	2403 140	Request for oral hearing	
1451 1,510	2451 755	Petition to institute a public use proceeding	
1452 110	2452 55	Petition to revive - unavoidable	
1453 1,300	2453 650	Petition to revive - unintentional	
1501 1,300	2501 650	Utility issue fee (or reissue)	
1502 470	2502 235	Design issue fee	
1503 630	2503 315	Plant issue fee	
1460 130	2460 65	Petitions to the Commissioner	
1807 50	2807 25	Processing fee under 37 CFR 1.17(q)	
1806 180	2806 90	Submission of Information Disclosure Stmt	
8021 40	28021 20	Recording each patent assignment per property (times number of properties)	
1809 750	2809 375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810 750	2810 375	For each additional invention to be examined (37 CFR 1.129(b))	
1801 750	2801 375	Request for Continued Examination (RCE)	
1802 900	2802 450	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$)

SUBMITTED BY

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(Complete if applicable)

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Signature

R Vasl

Date

07-21-2003

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This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PROVISIONAL PATENT APPLICATION

Inventor: MORDECHAI DEUTSCH

Title: AN EXPANDABLE CELL CHIP MATRIX

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to functional cellomics and, more particularly, to a method for the observation and manipulation of individual cells and their specific identified offsprings.

Combinatorial (bio)chemistry has evolved as an essential practical means permitting synthesis of many biologically-active and pharmaceutical structures, which must then be tested for their effects on animals and humans. The use of single, individual cell-based assays is an important tool in modern and advanced biomedical studies. Furthermore, cell functions are comprised of many interconnecting signaling and feedback pathways. Many times, a compound study based on isolated targets or cell preparations can not resolve this complexity. Thus, for a comprehensive understanding of a compound effect, testing of a single, whole living cell, is required. Such tests, in addition to their assistance in discovering and developing safer products, provide a useful tool in detecting biological and toxic effects, suggesting an alternative method for present toxicological tests resulted in reducing the number of animals used for testing.

In PCT patent application number WO 03/035824 to Deutsch filed 25 October 2001 there is described an example of an ordered matrix of wells configured for housing individual cells (cell chip) such as an interactive transparent individual cells biochip processor (ITICBP) that allows for the observation and manipulation of single cells in their own individual wells. A transparent cell chip enables performance of digital image analysis both on-line and off-line. The essence of the ITICBP methodology to Deutsch is the confinement of a single cell into

a designed restricted space (micro-micro-liter-well) which allows multiple stages of manipulation and testing within the pico-liter-wells, among which static and kinetic measurements under various manipulations.

However this unique capability is a significant drawback when one is interested in the proliferation of one or more of the selected individual cells following multiple stages of manipulation and testing within the pico-liter-wells.

There is however a drawback associated with Deutsch's method. In Deutsch's method the cell chip offers a means for working and for observing individual cells. The cell chip can be used to select cells that would be used for cloning among the total population of cells that may be positioned in the wells of the cell chip. However when the cell for cloning has been selected it is difficult to clone as there is only enough room for an individual cell in each well and as a result the cell would have to be transferred to another position for cloning. This transferring is difficult and adds possible complication with these additional manipulations. The method of limiting dilution is widely used today for isolating individual cells for cloning and it is not a precise method due to the fact that the process as a whole is totally random, the father cell cannot be preidentified, and loss of cells occur during dilution and during suspension pouring into the microplate wells. Additionally there is no way to ensure the existence of only a single cell in a well if at all.

There is thus a widely recognized need for, and it would be highly advantageous to have, a method that separates individual cells by their localization via a proper well size - while later on supplying each of the tens of thousands of individual cells, enough "individual space" which will allow each of them, simultaneously, to proliferate while keeping their clone identity. In other words, there is a need to have only one identified cell in a given (known) well to start off with and on the other hand there is a need to have enough room for proliferation and all of this on the scale of many thousands of cells each in their own identifiable and accessible location on a cell chip. Furthermore following proliferation of the identified cells an accurately defined harvesting of specific clones made from the selected individual cells is required, while preserving at least a portion of the particular clone in a well defined location.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawing. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawing:

FIG. 1 is a perspective top view of an unexpanded cell chip;

FIG. 2 is a perspective top view of an expanded cell chip following expansion; and

FIG. 3 is a perspective top view of an expanded cell chip following expansion and cell proliferation.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of an expandable interactive transparent individual cells biochip processor (cell chip) used for the cloning of pre investigated and selected individual cells.

The principles and operation of an expandable cell chip according to the present invention may be better understood with reference to the drawing and accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The

invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Referring now to the drawings, Figure 1 illustrates a portion of a cell chip 10. A cell chip 10 according to the prior art of Deutsch includes a glass or a rigid plastic cell chip unit 10. A cell chip 10 according to the present invention is composed at least in part by an expandable element such as an elastic silicone rubber, or a plastic paraffin film. The size and number of the wells may vary as desired for example 50x50 wells of 20 μm diameter. The depth of the wells may be for example 10-20 μm .

After individual cells 22 have been loaded, identified and examined in individual wells of the unexpanded cell chip 10 for cloning, the cell chip 10 is expanded to a size that will enable enough room in each well to undergo separate clonal proliferation that will preserve the original identity and known address which enables the recovery of specific representative cells from each clone with the possibility of leaving at least some of the cells in their identifiable location.

Cells 22 illustrated in Figures 1 and 2 may be of any shape or size and are not necessarily attached to the bottom of the cell chip wells. The wells 20 may be of varying sizes to accommodate cells of any shape or size. Cells 22 in Figure 3 should preserve their own shape and size within each well 20 following clonal proliferation.

The expansion can be performed either manually or automatically by any one of numerous methods known to those skilled in the art in the plastic/elastic industry. A radial expansion as illustrated in Figure 1 is only an example of an expansion. A simpler expansion could be asymmetric, for example in one dimension. As a result of this asymmetric procedure, the physical direction of the cellular proliferation may be dictated due to the fact that the cellular well can be made in any required shape or form which will the cell proliferation will follow.

Figure 2 is an illustration of the cell chip 10 in the stretched form showing a single cell 22 in each expanded (macro) well 20. The stretched wells now have room for cellular proliferation while maintaining its relative position. Figure 3 illustrates the cell chip 10 in the stretched form with cells that have undergone cellular proliferation with each well 20 containing a multiplicity of cells possessing the characteristics of the first cell in that particular well.

In a further embodiment of the present invention the contents of the expanded or stretched cell chip (Figure 2 and 3) may be placed in another plate by selecting at least some of the cells and transferring them with the use of for example micro capillaries or by optical tweezers, or by placing the other plate on top of the expanded chip and then inverting the two such that some or all of the contents may be transferred to the other plate. In a further embodiment another plate may be used for additional step of expansion to further expand the well areas for further proliferation and so forth. This replication process enables the expansion of the wells to continue to sizes unobtainable by a single stretch of the first plate. The abovementioned inverting method enables simultaneous manipulation in a high throughput process and under an improved sterile environment. Following expansion, a gel layer may be placed on top of the proliferated cells such that the cells may grow into the gel and be further manipulated. A gel film may enable to observe the cells to provide necessary nutrients, markers and/or drugs to examine characteristic secretions of individual populations of cloned cells.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the present specification.

WHAT IS CLAIMED:

1. An expandable cell chip essentially as described hereinabove or pictured in the figures.

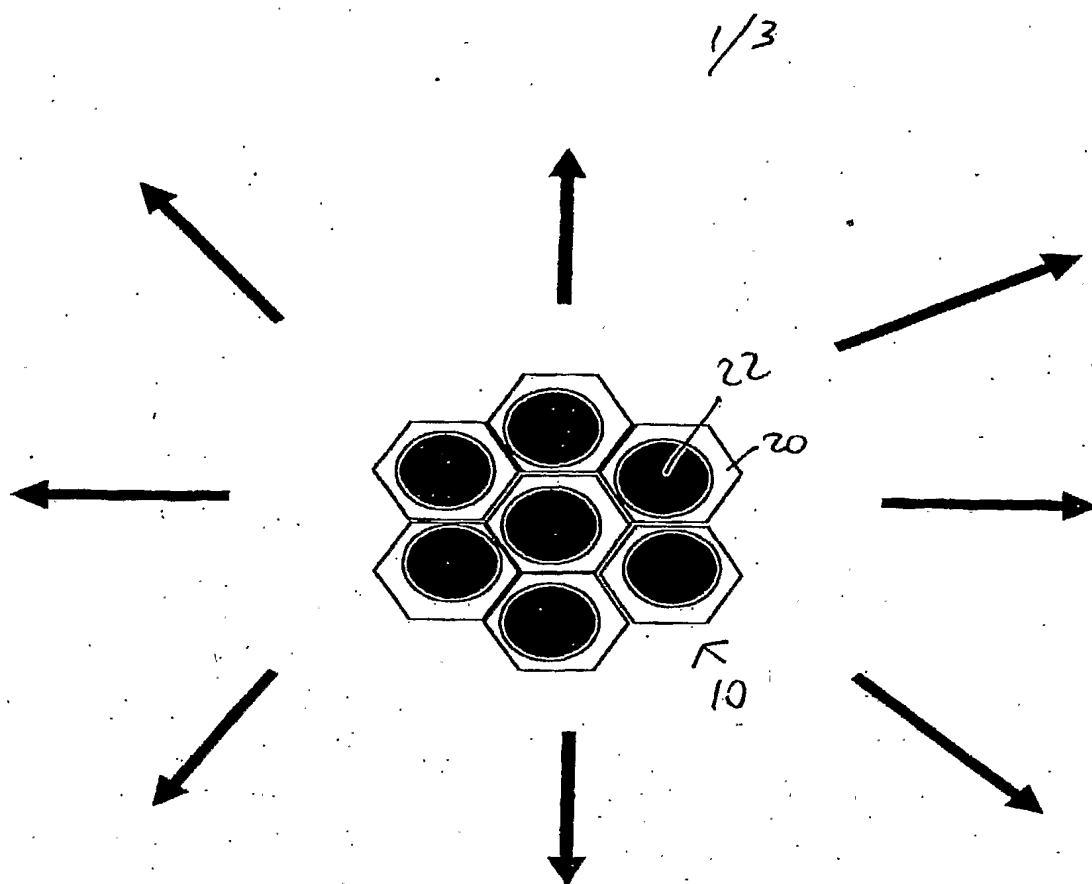


Figure 1

2/3

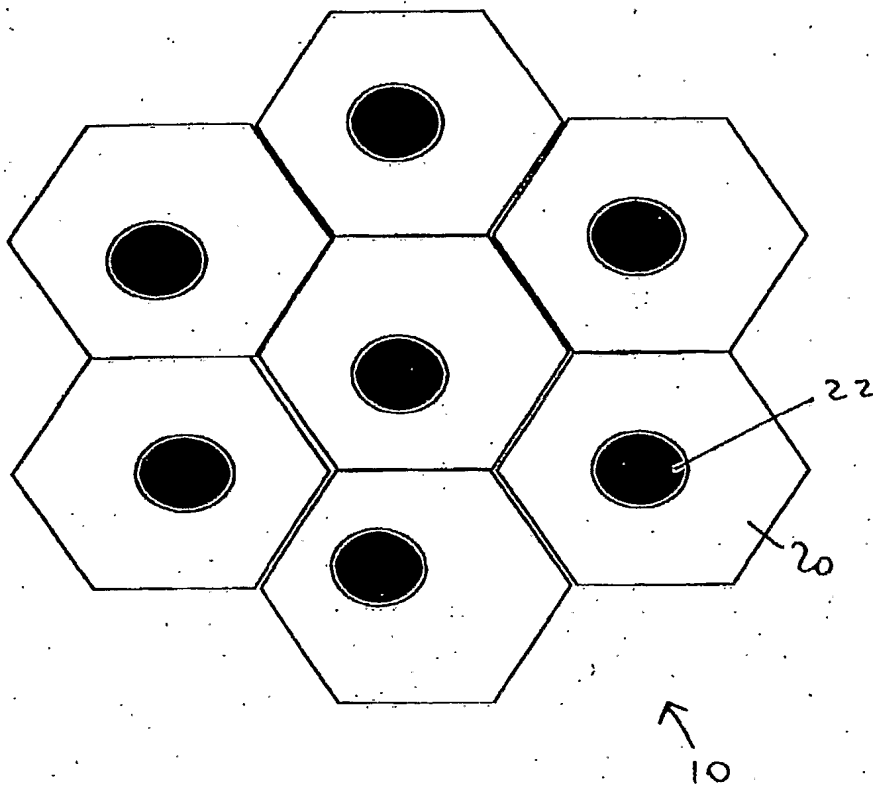


Figure 2

3/3

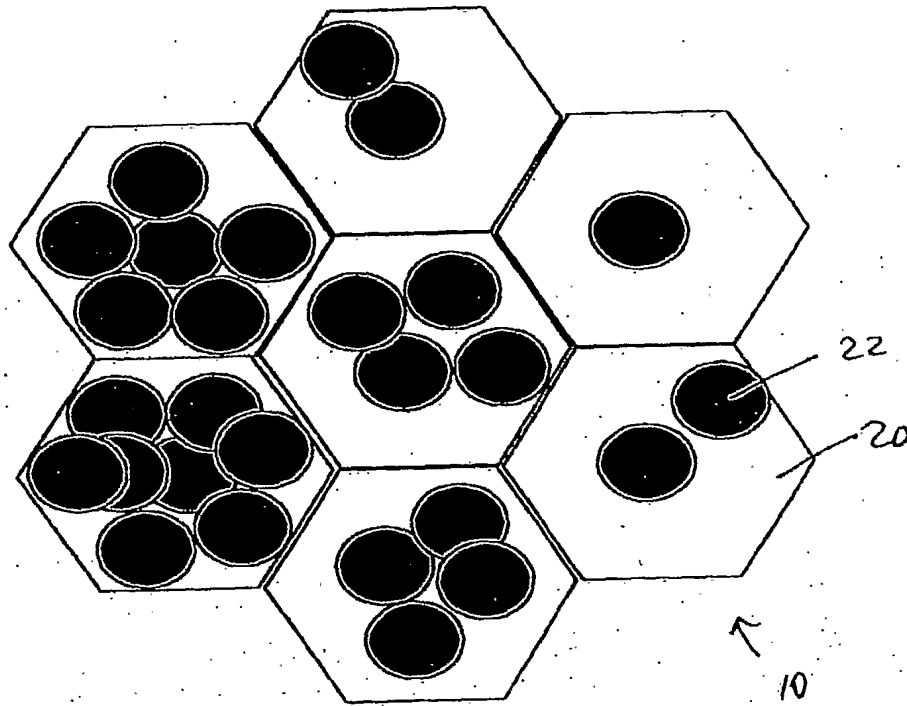


Figure 3